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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,074	11/28/2005	Graham Edmund Kelly	Q87092	4042

23373 7590 12/16/2008
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EXAMINER	
SEAMAN, D MARGARET M	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
12/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,074	KELLY ET AL.	
	Examiner	Art Unit	
	D. Margaret Seaman	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12 and 15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-12 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/26/07,4/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application was filed 11/28/2005 and is a 371 of PCT/AU03/1446 (11/3/2003) which claims priority to AU 2002952453 (11/1/2002). Claims 2-12 and 15-19 are before the Examiner.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claim 2 is rejected under 35 U.S.C. 101 because the claimed invention has been amended to contain a proviso that does not have support in the originally filed specification. This is new matter and needs to be withdrawn.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 7, 8, 12 and 15 are rejected under 35 U.S.C. 112, 1st paragraph, because the specification, while possibly being enabling for treating specific diseases, does not reasonably provide enablement for preventing diseases . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing

any of these diseases. The only established prophylactics are vaccines not the compounds such as presently claimed. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit the symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) As discussed above, preventing diseases required identifying those patients who will acquire the disease before the disease occurs. This would require extensive and potentially open-ended clinical research on healthy subjects. B) The passage spanning lines of the instant specification, lists the diseases applicant intends to prevent. C) There are no working examples of such preventive procedure in a man or animal in the specification. D) The claims rejected are drawn to the medical prevention and are therefore physiological in nature. E) The state of the art is that no general procedure is art-recognized for determining which patients generally will become afflicted with disease before the fact. F) The artisan using Applicant's invention would be a board certified physician who specializes in treating diseases. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, In

re Ferens, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of the practitioners in that art, Genetech vs. Novo Nordisk, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent diseases generally. That is, the skill is so low that no compound effective generally against diseases has ever been found let alone one that can prevent such conditions. G) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 214 (CCPA 1970). H) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by formula (I).

The Examiner suggests deletion of the word "prophylaxis".

5. Claims 7-12 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not adequately describe the nexus between the cellular activity of the instant compounds and a useful treatment of a disease/condition. Modulation of a receptor involves antagonism, inhibition, agonism and others. These modulations are sometimes opposite reactions to the same receptor. It is not seen where the

instant specification adequately describes the nexus between the cellular activity and a useful treatment of a single disease or condition.

6. Claims 7-12 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims,
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The nature of the invention is the method of treating a disease (generically) or a disease associated with aberrant cell survival, aberrant cell proliferation,

abnormal cellular migration, abnormal angiogenesis, abnormal estrogen/androgen balance, dysfunctional or abnormal steroid genesis, degeneration, inflammation and immunological imbalance, apoptosis in cells, migration of cells and angiogenesis in tissue.

The state of the prior art: The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all diseases, whether or not the modulation of androgen receptors would make a difference in the disease. Hence, in the absence of a showing of a nexus between any and all known diseases and the modulation of androgen receptors, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of modulation of androgen receptors. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of

the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for

more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

The presence or absence of working examples: There are 5 cell line tests on three compounds in the instant specification. However, there are no real world examples of the instant compounds treating diseases or cancer generally or any of the other conditions listed in the claims.

The amount of direction or guidance present: The guidance present in the specification is that of the compounds are related to known flavones and therefore should be able to treat any condition listed in the claims. Naturally occurring plant isoflavones are known to possess a wide range of fundamental biological effects on human cells including anti-oxidation and the up-regulation and down-regulation of a wide variety of enzymes and signal transduction mechanisms. Therefore, anything that is related to these flavones should have biological activity.

The breadth of the claims: The claims are drawn to the treatment of any and all diseases as well as a disease associated with aberrant cell survival, aberrant cell proliferation, abnormal cellular migration, abnormal angiogenesis, abnormal estrogen/androgen balance, dysfunctional or abnormal steroid genesis, degeneration, inflammation and immunological imbalance, apoptosis in cells, migration of cells and angiogenesis in tissue.

The quantity of experimentation needed: The quantity of experimentation needed is undue. One skilled in the art would need to determine what diseases out of all known diseases would be benefited and then would further need to determine which of the claimed compounds would provide treatment of the disease.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of claim 1 for the treatment of any disease. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

This rejection can be overcome by deleting the claims.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 6-8, 12 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7, 8 and 15 treat "diseases" or "diseases associated with" other conditions. Are all known diseases treatable by claims 7 and 15? What diseases are associated with the conditions listed in claim 8? How associated with these conditions must a condition be to be treatable by claim 8? Clarification is required.

Claim 6 appears to be missing essential steps for the process being claimed.

Claims 7-8, 12 and 15 "ameliorate" diseases. What is the extent of "ameliorate"? What are the metes and bounds of "ameliorate"?

Claim 15, is this drawn to a method of treating? Or to a pharmaceutical composition? Clarification is required.

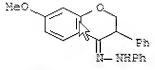
Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

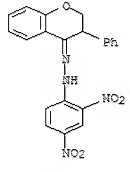
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 2-12 and 15-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Inoue CA 58:33237 & CA 58:33236), Donnelly, Ramanujam, Lebreton, Fukami, Cieslak and Bradbury. Inoue teaches

RN 100435-21-0 CA
CN 4H-1-Benzopyran-4-one, 2,3-dihydro-7-methoxy-3-phenyl-, 2-phenylhydrazone (CA INDEX NAME)



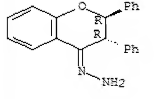
RN 89286-01-1 CA
CN 4H-1-Benzopyran-4-one, 2,3-dihydro-3-phenyl-, 2-(2,4-dinitrophenyl)hydrazone (CA INDEX NAME)



and . Donnelly teaches

RN 36944-54-4 CA
CN 4H-1-Benzopyran-4-one, 2,3-dihydro-2,3-diphenyl-, hydrazone, trans- (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry unknown.



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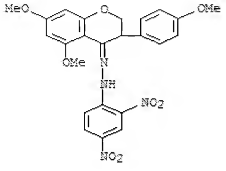
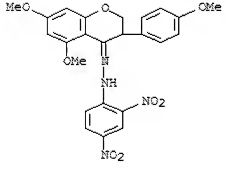
Rajanujam teaches

RN 122701-70-6 CA
CN 4H-1-Benzopyran-4-one, 2,3-dihydro-5,7-dimethoxy-3-(4-methoxyphenyl)-, 2-(2,4-dinitrophenyl)hydrazone (CA INDEX NAME)



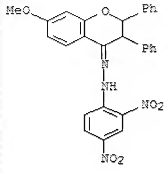
Lebreton teaches

RN 122701-70-6 CA
CN 4H-1-Benzopyran-4-one, 2,3-dihydro-5,7-dimethoxy-3-(4-methoxyphenyl)-, 2-(2,4-dinitrophenyl)hydrazone (CA INDEX NAME)



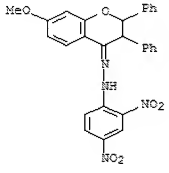
Fukami teaches

RN 115001-28-0 CA
CN 4H-1-Benzopyran-4-one, 2,3-dihydro-7-methoxy-2,3-diphenyl-, 2-(2,4-dinitrophenyl)hydrazone (CA INDEX NAME)



. Cieslak

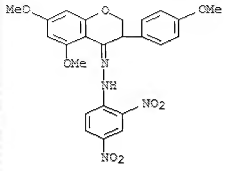
RN 115001-28-0 CA
CN 4H-1-Benzopyran-4-one, 2,3-dihydro-7-methoxy-2,3-diphenyl-, 2-(2,4-dinitrophenyl)hydrazone (CA INDEX NAME)



teaches .

Bradbury teaches

RN 122701-70-6 CA
CN 4H-1-Benzopyran-4-one, 2,3-dihydro-5,7-dimethoxy-3-(4-methoxyphenyl)-, 2-(2,4-dinitrophenyl)hydrazone (CA INDEX NAME)



These anticipate the instant claims.

Claim Objections

11. Claims 3, 5-6, 18 and 19 are objected to because of the following informalities: Claim 3 depends from claim 1 which is canceled. Claim 6 depends from claims 1 and 2. Claim 1 has been canceled. Claim 5 depends from claim 34. There is no claim 34. Claim 18 must be complete as written. Please clearly identify by name or structure the compounds that are encompassed by this claim. Claim 19 has a phrase "which compounds include". What does this mean?. Appropriate correction is required.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Margaret Seaman whose telephone number is 571-272-0694. The examiner can normally be reached on 730am-4pm, Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D. Margaret Seaman/
Primary Examiner, Art Unit 1625